

CLAIMS

1. A solid pharmaceutical composition comprising an active ingredient selected among tacrolimus and analogues thereof, wherein less than 20% w/w of the active ingredient is released within 0.5 hours, when subjected to an in vitro dissolution test using USP Paddle method and using 0.1 N HCl as dissolution medium.
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2. The solid pharmaceutical composition according to claim 1, wherein less than 20% w/w of the active ingredient is released within 3 hours.
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3. The solid pharmaceutical composition according to claim 1, wherein less than 10% w/w of the active ingredient is released within 3 hours.
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4. The solid pharmaceutical composition according to claim 1, wherein at least 50 % w/w of the active ingredient is released within 4 hours when subjected to an in vitro dissolution test using USP Paddle method and using 0.1N HCl as dissolution medium during the first 2 hours and then using a dissolution medium having a pH of 6.8.
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5. The solid pharmaceutical composition according to claim 1, wherein at least 50 % w/w of the active ingredient is released within 2.5 hours when subjected to an in vitro dissolution test using USP Paddle method and using 0.1N HCl as dissolution medium during the first 2 hours and then using a dissolution medium having a pH of 6.8.
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8. A solid pharmaceutical composition according to claim 1, wherein less than 50 w/w% of the active pharmaceutical ingredient is released within 8 hours, preferably within 15 hours, when subjected to an in vitro dissolution test using USP Paddle method and an aqueous dissolution medium adjusted to pH 4.5 with 0.005% hydroxypropylcellulose.
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9. The composition according to claim 8, wherein less than 40 w/w% of the active pharmaceutical ingredient is released within 8 hours, preferably within 15 hours.
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10. The composition according to claim 1, which is designed to substantially avoid CYP3A4 metabolism in the gastrointestinal tract upon oral administration.
11. The composition according to claim 10, wherein the composition is coated with an enteric coating.

12. The composition according to claim 1 comprising a solid dispersion or solid solution of active ingredient in a hydrophilic or water-miscible vehicle and one or more modifying release agents.

5 13. The composition according to claim 1, wherein the active ingredient is dispersed or dissolved in a hydrophobic vehicle.

14. The composition according to claim 13, wherein the hydrophobic vehicle is an oil, an oily material, a wax or a fatty acid derivative.

10 15. The composition according to claim 14, wherein the hydrophobic vehicle is selected from the group consisting of straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as stearic acid, myristic acid, palmitic acid, higher alcohols such as cetanol, stearyl alcohol, 15 low melting point waxes such as glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetyl monoglycerides; NVP polymers, PVP polymers, acrylic polymers, and mixtures thereof.

20 16. The composition according to claim 15, wherein the hydrophobic vehicle is glyceryl monostearate (GMS).

25 17. The composition according to claim 12, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyethylene glycols, polyoxyethylene oxides, poloxamers, polyoxyethylene stearates, poly-epsilon caprolactone, polyglycolized glycerides such as Gelucire®, and mixtures thereof.

30 18. The composition according to claim 12, wherein the hydrophilic or water-miscible vehicle is selected from the group consisting of polyvinylpyrrolidones, polyvinyl-polyvinylacetate copolymers (PVP-PVA), polyvinyl alcohol (PVA), polymethacrylic polymers (Eudragit RS; Eudragit RL, Eudragit NE, Eudragit E), cellulose derivatives including hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, pectins, cyclodextrins, galactomannans, 35 alginates, carragenates, xanthan gums and mixtures thereof.

19. The composition according to claim 12, wherein the vehicle is a polyethylene glycol (PEG).

20. The composition according to claim 12, wherein the polyethylene glycol has an average 5 molecular weight of at least 1500.

21. The composition according to claim 12 comprising a mixture of two or more hydrophilic or water-miscible vehicles.

10 22. The composition according to claim 12, wherein the mixture comprises a polyethylene glycol and a poloxamer in a proportion of between 1:3 and 10:1, preferably between 1:1 and 5:1, more preferably between and 3:2 4:1, especially between 2:1 and 3:1, in particular about 7:3.

15 23. The composition according to claim 12, wherein the poloxamer is poloxamer 188.

24. The composition according to claim 12, wherein the polyethylene glycol has an average molecular weight of about 6000 (PEG6000).

20 25. The composition according to claim 1 which further comprises one or more modifying release agents selected from the group consisting of water-miscible polymers, water-insoluble polymers, oils and oily materials.

25 26. The composition according to claim 25, wherein the water-insoluble polymer is selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose nitrate, and mixtures thereof.

30 27. The composition according to claim 26, wherein the oil or oily material is hydrophilic and selected from the group consisting of polyether glycols such as polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers; polyglycolized glycerides such as Gelucire® and mixtures thereof.

35 28. The composition according to claim 27, wherein Gelucire® is selected among Gelucire® 50/13, Gelucire® 44/14, Gelucire® 50/10, Gelucire® 62/05 and mixtures thereof.

29. The composition according to claim 25, wherein the oil or oily material is hydrophobic and selected from the group consisting of straight chain saturated hydrocarbons, sorbitan esters,

paraffins; fats and oils such as cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as stearic acid, myristic acid, palmitic acid, higher alcohols such as cetanol, stearyl alcohol, low melting point waxes such as glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or

5 unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, and mixtures thereof.

10 30. The composition according to claim 25, wherein the oil or oily hydrophobic material has a melting point of at least about 20°C.

31. The composition according to claim 25, wherein the water-miscible polymer is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC),

15 hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, poloxamers, polyoxyethylene stearates, poly- ϵ -caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA, polymethacrylic polymers and polyvinyl alcohol (PVA), poly(ethylene oxide) (PEO) and mixtures thereof.

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32. The composition according to claim 31, wherein the polymethacrylic polymers are selected among Eudragit® RS, Eudragit® RL, Eudragit® NE and Eudragit® E.

25 33. The composition according to claim 11, which is entero-coated using a water-miscible polymer having a pH-dependant solubility in water.

34. The composition according to claim 33, wherein the water-miscible polymer is selected from the group consisting of polyacrylamides; phthalate derivatives such as acid phthalates of carbohydrates including amylose acetate phthalate, cellulose acetate phthalate, cellulose

30 acetate terephthalate, cellulose acetate isophthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropyl cellulose phthalate, hydroxypropylcellulose acetate phthalate, hydroxypropyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate (HMPCP), methylcellulose phthalate, methyl cellulose acetate phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch 35 acid phthalate; phthalates of other compounds including polyvinyl acetate phthalate (PVAP); other cellulose derivatives including hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethylcellulose, cellulose acetate trimellitate; alginates; carbomers;

polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, methacrylic acid copolymers (for example Eudragit® L and Eudragit® S); styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers; shellac, starch glycolate; polacrylin; vinyl acetate and crotonic acid copolymers and mixtures thereof.

35. The composition according to claim 1 which further comprises one or more pharmaceutically acceptable excipients.

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36. The pharmaceutical composition according to claim 35, wherein the pharmaceutically acceptable excipients are selected from the group consisting of fillers, diluents, disintegrants, binders and lubricants.

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37. The pharmaceutical composition according to claim 35 in particulate form, for example in powder form.

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38. The pharmaceutical composition according to claim 35, wherein the particles have a geometric weight mean diameter d_{gw} from about 10 μm to about 2000 μm , preferably from about 20 μm to about 2000 μm , especially from about 50 μm to about 300 μm .

39. The pharmaceutical composition according to claim 35, wherein the particles have a geometric weight mean diameter d_{gw} from about 50 μm to about 300 μm .

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40. A dosage form comprising the pharmaceutical composition according to claim 35, which is a solid oral dosage form.

41. The dosage form according to claim 40, which is a unit dosage form.

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42. The dosage form according to claim 40, which further comprises a pharmaceutically acceptable additive selected from the group consisting of flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents and absorption enhancing agents.

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43. The dosage form according to claim 40, wherein at least one pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt

thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

- 5 44. The dosage form according to claim 40, wherein at least one pharmaceutically acceptable excipient is a silica acid or a derivative or salt thereof.
- 10 45. The dosage form according to claim 40, wherein at least one pharmaceutically acceptable excipient is silicon dioxide or a polymer thereof.
- 15 46. The dosage form according to claim 45, wherein the silicon dioxide product has properties corresponding to Aeroperl® 300, (available from Degussa, Frankfurt, Germany).
- 20 47. Use of the oral pharmaceutical composition according to claim 1 to enhance the oral bioavailability of tacrolimus.
- 25 48. Use of the solid composition according to claim 1 for the preparation of an oral dosage form, preferably tablets, capsules or sachets.
- 30 49. Use of the solid composition according to claim 1 for the preparation of granules, pellets microspheres or nanoparticles.
50. Use of the solid composition according to claim 1 for the preparation of a controlled or modified release solid dosage form.
51. Use of the solid composition according to claim 1 for the preparation of a delayed release solid dosage form.
52. Use of the solid composition according to claim 1 for the preparation of a topical dosage form.
53. A method for the preparation of the composition according to claim 12, the method comprising the step of dissolving or dispersing tacrolimus or an analogue thereof in a hydrophilic vehicle to obtain a solid solution or dispersion at ambient temperature.